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CLINICAL INVESTIGATION

Renal function following acute renal failure in childhood: A long term follow-up study

HELEN N. GEORGAKI-ANGELAKI, DAVID B. STEED, CYRIL CHANTLER, and GEORGE B. HAYCOCK

Department of Paediatric Nephrology and Urology, United Medical and Dental Schools of Guy's and St Thomas's Hospitals (Guy's Campus), Guy's Hospital, London SE1 9RT, England

Renal function following acute renal failure in childhood: A long term follow-up study. We measured glomerular and tubular function in 10 children, aged 7 to 19 years, 7 to 12 years after apparent recovery from their episodes of acute renal failure. Although glomerular filtration rate was normal in all, filtration fraction (inulin clearance/PAH clearance) was elevated in six of eight patients. Segmental tubular sodium transport was assessed using clearance techniques during hypotonic saline diuresis; both proximal and distal sodium reabsorption were normal when compared with age-appropriate normal standards. Tubular reabsorption of phosphate, glucose and amino acids were also normal, as were urinary concentrating and diluting capacity and distal tubular hydrogen ion secretion. We conclude that, despite normal glomerular filtration rate, glomerular function is abnormal in a significant number of children who have apparently recovered completely from ARF, probably due to destruction of a proportion of the total nephron population, predominantly those located in the superficial layers of the cortex.

Since the introduction of peritoneal and extracorporeal dialysis as routine forms of treatment for acute renal failure (ARF), clinical recovery has been the expected outcome in the majority of patients without concomitant failure of other organ systems. However, several studies have shown that recovery in adults is not always accompanied by restoration of normal renal function; residual abnormalities of both glomerular and tubular function have been described [1–5]. Many adults developing ARF do so against a background of known risk factors including hypertension, diabetes mellitus, pre-existing renal disease and advancing age [6], which might be expected to impair renal recovery. The relative absence of these, and the different spectrum of causes of ARF in children as compared with adults [7], means that conclusions based on findings in adult patients cannot safely be extrapolated to children. No detailed studies of renal function in children who have apparently recovered from ARF have been published.

We therefore measured glomerular and tubular function in 10 children, 7 to 12 years after recovery from an episode of ARF severe enough to require dialysis.

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Methods

Patients and control subjects

Of 37 children treated for ARF at Guy's Hospital between 1971 and 1975 [7] and who had been judged to have recovered completely, 10 were located 7 to 12 years later and agreed to participate in the study. All had received peritoneal or extracorporeal dialysis. Details including age at presentation, diagnosis, type and duration of dialysis and renal function at discharge from hospital are given in Table 1. All patients were clinically well at discharge and have remained so since. Apart from dialysis only supportive treatment was given, with the exception of the boy with Schönlein-Henoch purpura who was treated with prednisolone, azathioprine, aspirin and dipyridamole for two years.

Two control groups were used, designated C1 and C2, respectively. Group C1 comprised six healthy volunteers, four men and two women aged 20 to 30 years, who were studied in our laboratory following the same protocol as the patients. Because current ethical constraints did not allow us to study healthy children, we also compared the results obtained from our patients with those previously published by Rodriguez-Soriano et al [8] based on studies of 17 normal children, aged 2 to 12 years, using identical methods.

In examining the relationship between glomerular filtration rate (GFR) and renal plasma flow, data from the present study were combined with those extracted from earlier adult studies in which individual values for GFR and clearance of para-amino hippuric acid (C_{PAH}) were tabulated [2, 4, 9].

The study was approved by the ethical committee of Guy's Hospital and Medical School. Informed consent was obtained from all the patients, and from the parents of those who were still under 16 years of age.

Clinical and laboratory methods

Each subject was studied over a two day period. On the first day a full physical examination was performed, including measurement of height, weight and blood pressure. A clean, voided urine specimen was examined by microscopy, dipstick testing for pH, glucose, protein and blood (Hema-combistix, Ames Laboratories) and bacteriological culture. A priming dose of inulin and PAH was then given intravenously (1 ml/kg of a solution made by mixing 50 ml of 10% inulin and 1 ml of 20%

Table 1. Clinical data from the 10 children studied

Patient no	Sex	Age at presentation	Diagnosis	Duration of dialysis	Renal function at discharge
1	M	3 weeks	Septicemia	2 days (P)	P_U 6 mmol/liter
2	F	3½ years	Post-cardiac surgery	2 days (P)	P_{Cr} 53 μmol/liter
3	M	6 years	Post-cardiac surgery; septicemia	25 days (H)	P_{Cr} 53 μmol/liter
4	M	10 years	S-H purpura; Intussusception	21 days (P) 14 days (H)	P_{Cr} 47 μmol/liter
5	F	4 years	HUS	21 days (P)	P_{Cr} 43 μmol/liter
6	M	1½ years	Septicemia	7 days (P)	P_U 10 mmol/liter
7	F	8 months	HUS	14 days (P)	P_{Cr} 48 μmol/liter
8	M	3 days	Prematurity; perinatal hypoxia	2 days (P)	P_{Cr} 60 μmol/liter
9	F	6 years	Post-cardiac surgery	4 days (P)	P_{Cr} 124 μmol/liter
10	M	10 years	HUS	28 days (H)	P_{Cr} 70 μmol/liter

Abbreviations are: S-H purpura, Schönlein-Henoch purpura; HUS, hemolytic uremic syndrome; (P) and (H) denote peritoneal dialysis and hemodialysis, respectively; P_U and P_{Cr}: plasma urea and creatinine.

PAH) followed by a constant infusion of the same solution at a rate of 1 ml/hr for every 5 ml/min estimated GFR [9]. Steady-state plasma PAH concentrations of 1 to 2 mg/dl were achieved in all cases. Simultaneously, hypotonic (0.45%) saline was infused according to the method of Rodriguez-Soriano et al [8]. Three or four timed urine collections, each lasting 20 to 30 minutes, were obtained during the infusion. A 5 ml heparinized blood sample was drawn at the approximate midpoint of each collection period, from the arm opposite that receiving the infusion. After completion of the clearance studies, a ^{99m}Tc DMSA (dimercaptosuccinic acid) scan was performed. Following a dry supper at 6 p.m., a 12-hour overnight period of water deprivation was imposed, at the end of which urinary osmolality was estimated [10].

On the second morning, following a normal breakfast, 3 mmol/kg sodium bicarbonate ($NaHCO_3$) dissolved in 280 to 300 ml tap water was given by mouth. Urine and venous blood samples were obtained at three, four and five hours after the $NaHCO_3$ load for measurement of pH and pCO_2.

On a separate occasion a 24-hour urine sample was collected from each patient, at the end of which a further blood sample was drawn in the fasting state; glucose, phosphate and creatinine concentrations were measured in blood and urine.

Inulin was measured by the method of Heyrovsky [11] and PAH by a modification of the method of Bratton and Marshall [12]. Sodium and potassium were measured by flame photometry, chloride by a coulombometric method using a Corning-Eel autoanalyzer and creatinine by an automated, reaction rate modification of the Jaffe reaction [13]. This method is subject to less interference from non-creatinine chromogen than the Jaffe reaction read at equilibrium, but still overestimates true creatinine to a small degree at normal plasma concentrations. Urine and whole blood pH and pCO_2 were measured on an Autocal Blood Gas Analyzer (Instrumentation Laboratories). Glucose was estimated by a glucose oxidase method, and phosphate on a Vickers M 300 automatic analyzer. Osmolality was estimated by freezing point depression using a Roebling automatic micro-osmometer.

Clearances of inulin (C_{In}), PAH (C_{PAH}), creatinine (C_{Cr}), sodium (C_{Na}) and chloride (C_{Cl}), as well as osmolar clearance (C_{Osm}), were calculated as UV/P, where U and P are respectively the urine and plasma concentrations of the substance and V the urine flow rate (ml/min). The quotient C_{In}/C_{PAH} is termed the filtration fraction (FF) for convenience and in deference to custom, although it is recognized that it may not measure 'true' FF if PAH extraction is incomplete (**Discussion**). The clearance of solute-free water (free water clearance, C_{H_2O}) was taken as $V\text{-}C_{Osm}$. Fractional tubular reabsorption of filtered phosphate (TRP) was derived from the formula:

$$TRP\ (\%) = [1 - (U_P \cdot P_{Cr}/U_{Cr} \cdot P_P)] \times 100$$

where the subscripts P and CR denote phosphate and creatinine, respectively. The theoretical renal phosphate threshold ($TmPO_4$/GFR) was calculated using the nomogram of Walton and Bijvoet [14].

Statistical analysis was done using Student's *t*-test and linear regression.

Results

Clinical findings

The study sample was comparable with the population of surviving children from which it was drawn as regards age, diagnosis, sex ratio, duration of dialysis and period of follow up (Table 1). All were physically well although two (cases 8 and 9) experienced some learning difficulties and one (case 10) had been diagnosed as suffering from minimal cerebral dysfunction. All lay between the 10th and 95th percentiles for height and weight, and all had normal blood pressure for age. No patient had proteinuria, macroscopic haematuria or evidence of urinary tract infection; however, four (cases 1, 4, 5 and 9) had persistent microscopic haematuria on both microscopy and dipstick testing.

Glomerular function

Individual values for inulin and PAH clearances (C_{In}, C_{PAH}) and for FF are presented in Table 2. Each tabulated value is the mean of three to four collection periods. C_{In} (mean ± SD) was

Table 2. Glomerular function in the 10 children, 7–12 years after AFR

Patient no	Age (years)	C_{IN}	C_{PAH}	FF
		ml/min/1.73 m^2		
1	12	118	401	0.29
2	13	127	766	0.16
3	16	77	166	0.46
4	18	157	—	—
5	11	81	446	0.18
6	12	135	492	0.27
7	7	137	382	0.35
8	7	123	473	0.26
9	15	115	—	—
10	19	160	539	0.29
$\bar{X}$ ± SD	13 ± 4	123 ± 28	458 ± 168	0.28 ± 0.09

Abbreviations are in the text.

123 ± 28 ml/min/1.73 m^2; C_{PAH} was 458 ± 168 ml/min/1.73 m^2; FF was 0.28 ± 0.09. These values were not significantly different from those obtained from three adults in group C1 (Table 3), however, two patients (cases 3 and 5) had borderline low values for C_{In}. In all but two cases (3 and 5) GFR had increased from the immediate post-ARF follow-up period to the present study, but in those two (cases 3 and 5) a slight decline was observed (Fig. 1). In Figure 2A, C_{In} is plotted on the ordinate against C_{PAH} on the abscissa; Figure 2B shows the same relationship with data from three other published studies added [2, 4, 9]. The continuous and interrupted lines represent the mean and normal range (±2 SD) for FF as reported by Smith [15]. In Figure 3, FF is plotted against duration of dialysis; a weak positive correlation is present but this does not quite achieve significance ($0.1 < P < 0.15$).

Tubular function

No patient had glycosuria or amino aciduria. The results of the clearance studies performed during hypotonic saline diuresis are shown in Table 3. The tabulated values for all results other than C_{In}, C_{PAH}, C_{Cr} and FF are those from the urine collection period showing the lowest urinary osmolality. No differences were seen between the patients and group C1 in any of the measured variables. However V, C_{H_2O}, the sum of C_{H_2O} and C_{Na} and the sum of C_{H_2O} and C_{Cl} (all factored by GFR) were lower in the patients than in group C2, despite comparable degrees of urinary dilution (U_{Osm} 62 ± 89 vs. 54 ± 13 mOsm/kg; P = NS). Figure 4 shows (C_{H_2O} + C_{Na})/dl GFR plotted against age for the patients, groups C1 and C2 and also the infants reported by Rodriguez-Soriano et al [8], age being scaled logarithmically. A significant negative correlation was found for the data taken as a whole ($r = -0.78$, $N = 56$, $P < 0.001$). A very close positive correlation was obtained between C_{H_2O} and V (Fig. 5A) and C_{H_2O} and the sum of C_{H_2O} and C_{Na} (Fig. 5B), no difference being found in this respect between patients and group C1 ($r = 0.99$, $N = 16$, $P < 0.001$ for both relationships). Table 4 shows the results of the overnight water deprivation test, measurement of TRP and $TmPO_4$/GFR and the urine-blood pCO_2 gradient [16].

Discussion

Between 1971 and 1975, 70 children aged from 3 days to 16 years were diagnosed as having ARF at Guy's Hospital (72 episodes of ARF); details of these patients have been published elsewhere [7]. Twenty-three failed to recover renal function (17 dead and 6 entering the end-stage renal failure program); of the remainder, 37 were judged to have normal renal function at discharge, while 10 survived with chronic renal failure of various degrees of severity. The paucity of published data on the long term prognosis for children who have apparently recovered completely from ARF prompted the present investigation, which was based on a sample of the 37 children who fulfilled conventional criteria for complete recovery: normal GFR or plasma creatinine concentration, normal blood pressure and absence of proteinuria. The 27 patients with apparently normal function at discharge who were not studied either were not located or refused to participate in the investigation. It is unlikely that any of these had entered chronic renal failure in the interval since their acute illness, since Guy's Hospital is the referral center for chronic, as well as acute, renal failure for the population from which these children were drawn, and had deterioration occurred they would almost certainly have been re-referred. There is therefore no reason to believe that the study sample differed in any systematic way from the group as a whole.

Several studies of the long term prognosis following ARF in adults have been published [1–5, 17, 18]. Most surviving patients were clinically well, asymptomatic and had returned to their former activities. However, GFR and C_{PAH} were found to be permanently reduced in some patients, implying that irreversible glomerular damage had occurred [1, 3–5, 18]. In addition, evidence of tubular dysfunction was found, particularly defects of urinary concentration and hydrogen ion secretion [1, 3, 17]. Similar evidence of tubular dysfunction was found by Stark and Geiger [19] in a study of infants who had survived an episode of ARF, attributed to vascular accidents in the newborn period. Progressive deterioration in renal function and loss of renal size have been observed following experimental ischaemic ARF in mice [20].

In the present study, tests of tubular function including concentrating and diluting ability, acid excretion and tubular reabsorption of phosphate, glucose and amino acids gave normal results. A mean peak urinary osmolality of 860 mOsm/kg H_2O after overnight water deprivation is slightly suboptimal by comparison with published standards. However, to achieve the values of >873 mOsm/kg H_2O reported by Edelmann et al [10] required 17 to 20 hours dehydration, whereas our patients were only thirsted for 12 hours. It is possible that a slight reduction in maximum concentrating ability was present in our patients, but if so it was minimal and without clinical significance.

Interpreting the results of the hypotonic saline diuresis is less straightforward, mainly because of the unexpected finding of a significant difference in fractional proximal tubular sodium and water reabsorption between the two control groups (Table 3). The most probable explanation of this discrepancy is age difference: our patients were younger than the adults who composed group C1, but significantly older than the children in group C2 [8]. If fractional distal sodium delivery (C_{H_2O} + C_{Na}/100 ml GFR) is plotted against age for all subjects and controls, the patients' results lie close to the line of the overall relationship, with one possible exception (Fig. 4). It therefore seems likely that the findings in our patients do not deviate significantly from age-corrected normal values. Sodium reabsorption in the distal nephron, expressed as a fraction of sodium deliv-

Table 3. Results of clearance studies in the patients and both control groups ($\bar{X} \pm SD$)

	Control group 1	←P→	Patients	←P→	Control group 2
N	6		10		17
Age *years*	23–33		6–19		2–12
C_{In} *ml/min/1.73 m²*	141 ± 18[a]	NS	123 ± 28	—	—
C_{PAH} *ml/min/1.73 m²*	690 ± 80[a]	NS	458 ± 168[b]	—	—
FF	0.2 ± 0.05[a]	NS	0.28 ± 0.08[b]	—	—
C_{Cr} *ml/min/1.73 m²*	134 ± 27	NS	124 ± 29	NS	125 ± 25
C_{H_2O} *ml/dl/GFR*	9.7 ± 2.9	NS	9.6 ± 2.9	<0.001	14.0 ± 2.6
U_{Osm} *mOsm/kg* H_2O	63 ± 7.6	NS	62 ± 8.9	NS	54 ± 13.3
V *ml/dl GFR*	12.3 ± 3.0	NS	12.2 ± 3.3	<0.001	17.0 ± 2.7
$C_{Na} + C_{H_2O}$ *ml/dl GFR*	10.9 ± 3.0	NS	10.8 ± 2.8	<0.001	15.3 ± 2.6
$C_{Cl} + C_{H_2O}$ *ml/dl GFR*	11.4 ± 3.0	NS	11.3 ± 2.8	<0.001	15.9 ± 2.6
$[C_{H_2O}/(C_{Na}+C_{H_2O})] \times 100$	85 ± 4.7	NS	88 ± 4.3	NS	90 ± 3.3

[a] Obtained from only three subjects in control group C1; [b] from 8 of the patients.

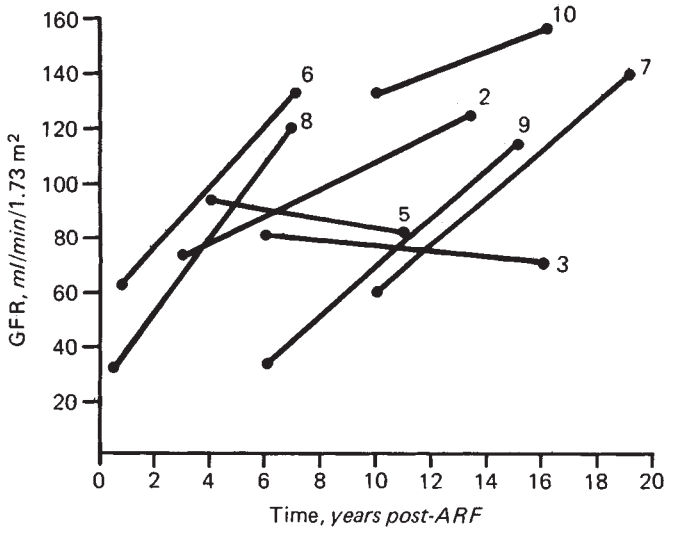

Fig. 1. *GFR calculated from the height/creatinine formula [9] at discharge from hospital and at entry into the study for the 8 children in whom plasma creatinine estimations were available at the relevant times.* The patients are numbered as in Tables 1 and 2.

ered to that segment, was normal at various levels of distal delivery measured either as $C_{H_2O}/(C_{H_2O} + C_{Na})$ or C_{H_2O}/V; there was no difference between our patients and either control group (Table 3, Fig. 5).

The mean values obtained for clearances of inulin, PAH and creatinine in the patients did not differ significantly from controls (Table 3). However, some individual values for PAH were unexpectedly low, yielding high values for FF (Table 2). When C_{PAH} was plotted against C_{In} (Fig. 2A), six of the eight data points fell above the upper limit (+2 SD) of the normal range as published by Smith [15]. When data from three, previously published adult series which reported individual values for GFR and C_{PAH} were added, the same trend was seen in all (Fig. 2B). At least three explanations might account for this finding. First, PAH extraction may have been incomplete because of plasma concentrations above the saturation point of the transport system. Second, diffuse nephron loss might lead to a compensatory increase in GFR by means of increased FF, as a result either of altered glomerular Starling forces leading to a rise in ultrafiltration pressure or of a change in the glomerular ultrafiltration coefficient. Third, selective destruction of part of the superficial nephron population, with relative sparing of the deep (juxtamedullary) nephrons, would lead to a situation in which, following recovery, a greater than normal proportion of total renal blood flow perfused the juxtamedullary nephrons. To the extent that these nephrons extract PAH inefficiently, due to bypassing of the proximal tubules by postglomerular blood, PAH clearance would therefore underestimate renal plasma flow and spuriously high values for FF would be given by the quotient C_{In}/C_{PAH}.

The first explanation is unlikely to be correct, because the plasma concentrations of PAH achieved in our study (1 to 2 mg/dl) were well below those at which the transport system becomes saturated. The second is also unconvincing, because in both clinical [21] and laboratory [22, 23] studies the increase in single nephron GFR measured in residual nephrons following nephrectomy, or nephrectomy plus segmental infarction of the remaining kidney, is accompanied by a parallel increase in blood flow without a change in FF. Support for the third interpretation is provided by the study of Rodriguez-Soriano et al [24], who found that diffuse cortical necrosis affected predominantly the juxtamedullary nephrons in the newborn but the superficial cortical nephrons in the adult. Other studies are in agreement as regards the distribution of the adult lesion [25]. The different pattern of damage observed in the two age groups studied by Rodriguez-Soriano et al [24] might be predicted from the known functional characteristics of different nephron subsets during development. In the newborn, the superficial cortical nephrons are functionally immature and receive only minimal blood flow [26, 27]. The susceptibility of nephrons to ischemic damage is proportionate to their metabolic activity and oxygen requirement [28]. The inactivity of the superficial nephron population in the newborn would be expected to afford protection, while the pre-eminence of this population in the transport activities of the adult kidney would, conversely, render it more vulnerable to anoxic and metabolic injury. The majority of the cases in our study were well outside the neonatal period at the time of the episode of ARF, and the intrarenal distribution of blood flow can be assumed to have conformed to the adult pattern. The exception to this was patient 8, who was a premature infant only three days old at the time of presentation. His FF was only slightly elevated (0.26); nevertheless, this single result weakens our interpretation somewhat. To test the hypothesis directly would necessitate measurement of PAH extraction, which unfortunately is too invasive a procedure for

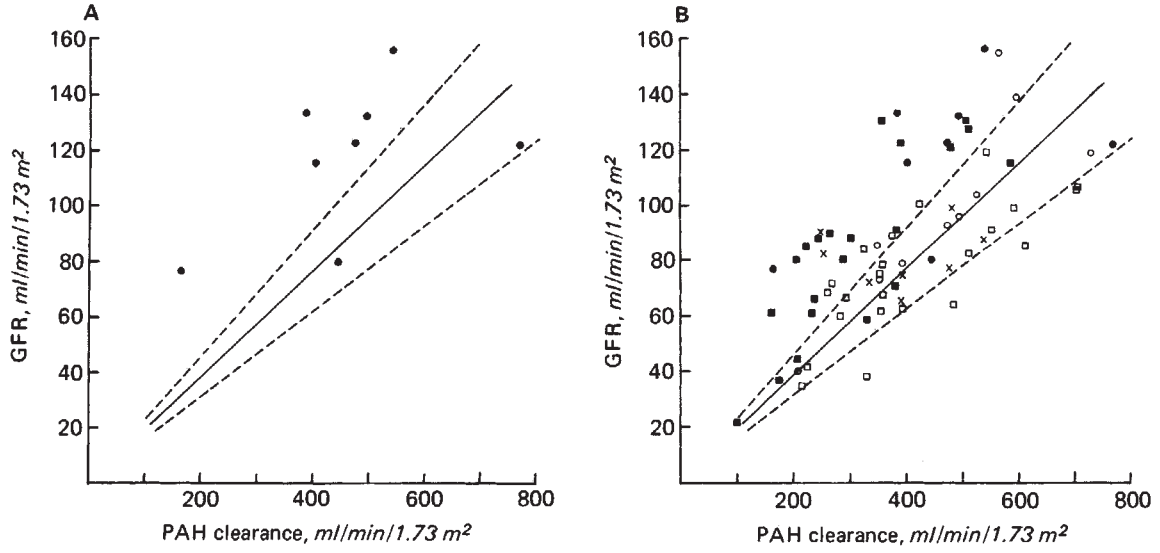

Fig. 2. A. *Inulin clearance on the ordinate plotted against PAH clearance on the abscissa for the 8 children in whom data were available.* **B.** As for (A), but with data from 3 other (adult) studies superimposed. Data taken from references [2] (open squares), [4] (closed squares, GFR measured as thiosulphate clearance; crosses, GFR measured as creatinine clearance) and [17] (open circles). Data from the present study are shown as closed circles. The continuous and interrupted lines show the mean ± 2 SD for filtration fraction in normal adults [15].

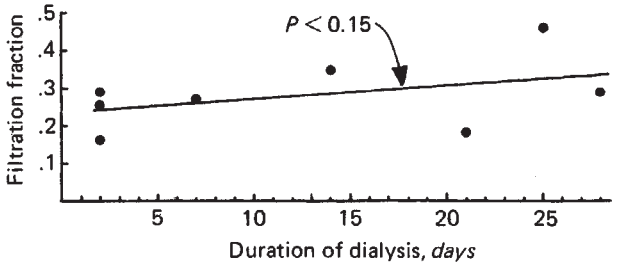

Fig. 3. *Filtration fraction (C_{In}/C_{PAH}) plotted against duration of dialysis.*

Table 4. Results of tests of urinary concentrating capacity, tubular phosphate reabsorption and hydrogen ion excretion

Test	*N*	$\bar{X}$ ± SD
Maximum U_{Osm} *mOsm/kg* H_2O	9	860 ± 80
TRP %	8	87.2 ± 5.7
$TmPO_4$/GFR *mmol/liter*	8	1.2 ± 0.11
U-B pCO_2 *mm Hg*[a]	7	34.3 ± 15.8

[a] U-B pCO_2 denotes urine-minus-blood carbon dioxide gradient.

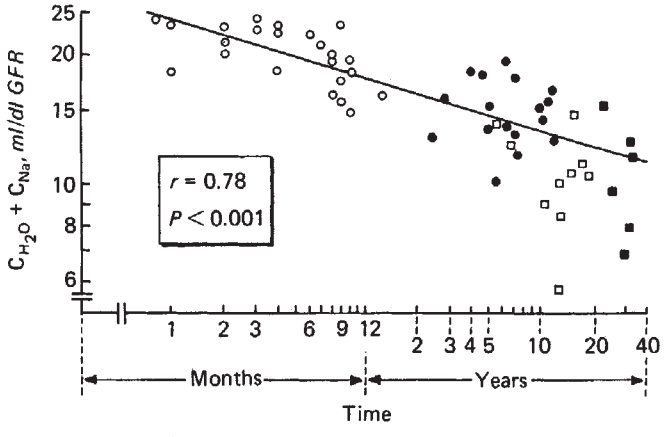

Fig. 4. *Estimated distal tubular delivery of sodium plotted against age.* Open and closed circles represent infants and children from the study of Rodriguez-Soriano et al [8]; closed squares, adult controls; open squares, patients.

clinical application to human subjects; in the meantime, our discussion of the cause should be regarded as speculative. We did not feel justified in recommending renal biopsy in this group of apparently fit patients since it was highly unlikely that the results would have conferred any benefit on them.

ARF was of mixed aetiology in the cases reported in this paper (Table 1); however, the course following initial recovery appeared similar in the various groups. Of the two children whose GFR's fell to borderline or slightly reduced values in the interval between ARF and the present study (cases 3 and 5), one had septicemia following cardiopulmonary bypass and the other had the hemolytic uremic syndrome. The weak correlation between duration of dialysis and eventual FF (Fig. 3), although not statistically significant, suggests that the severity of the initial injury, rather than its nature, in an important determinant of final outcome. This conclusion finds support in a previous study in which the histological severity of acute tubular necrosis was found to be significantly correlated with the duration of ARF [29]. Whether our hypothesis concerning the cause of the low FF, which was based on a study of hypoxic ARF [24], can be extended to cover the effects of ARF due to other causes, is unknown. However, immunological as well as hypoxic injury would presumably be expected to follow blood flow in its distribution, so similar morphological considerations should apply to both.

We conclude that normal growth and development, blood pressure, GFR and the absence of proteinuria following clinical recovery from ARF in infancy and childhood may conceal significant permanent renal damage. The reduced C_{PAH} and high FF found in some cases suggests that substantial nephron loss, predominantly affecting superficial cortical units, may

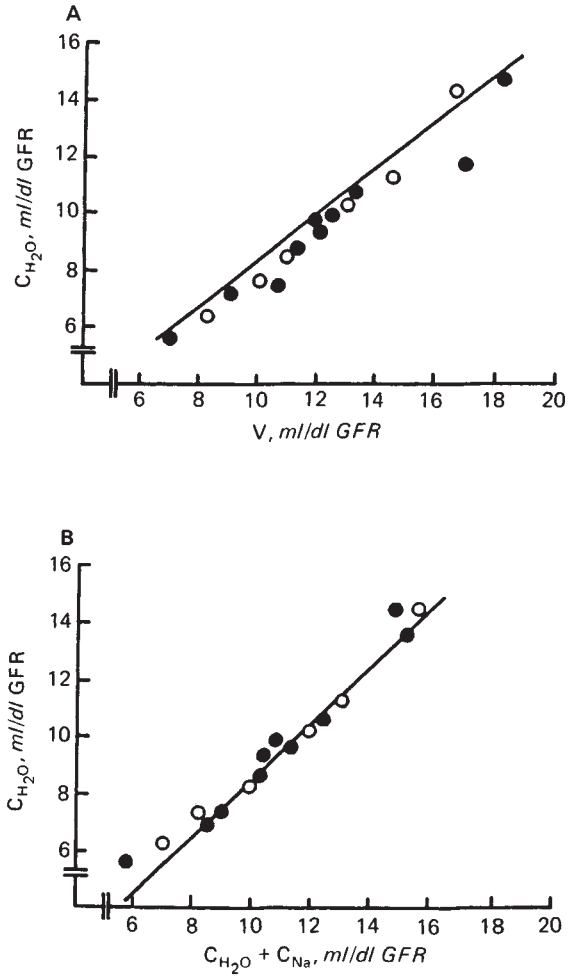

Fig. 5. *Free water clearance plotted against fractional distal delivery of filtered water, calculated as* **(A)** *urine flow rate and* **(B)** *the sum of sodium and free water clearance, respectively.*

occur while whole kidney GFR is maintained within the normal range by increasing single nephron GFR in surviving nephrons. Even in the absence of reduced GFR or evidence of tubular dysfunction, the kidneys should not be assumed to have escaped permanent damage unless PAH clearance, or an equivalent test of superficial nephron function, has been shown to be normal.

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Reprint requests to Dr. George B. Haycock, M.B., F.R.C.P., Guy's Hospital, St. Thomas's Street, London SE1 9RT, United Kingdom.

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